

Fig. 1

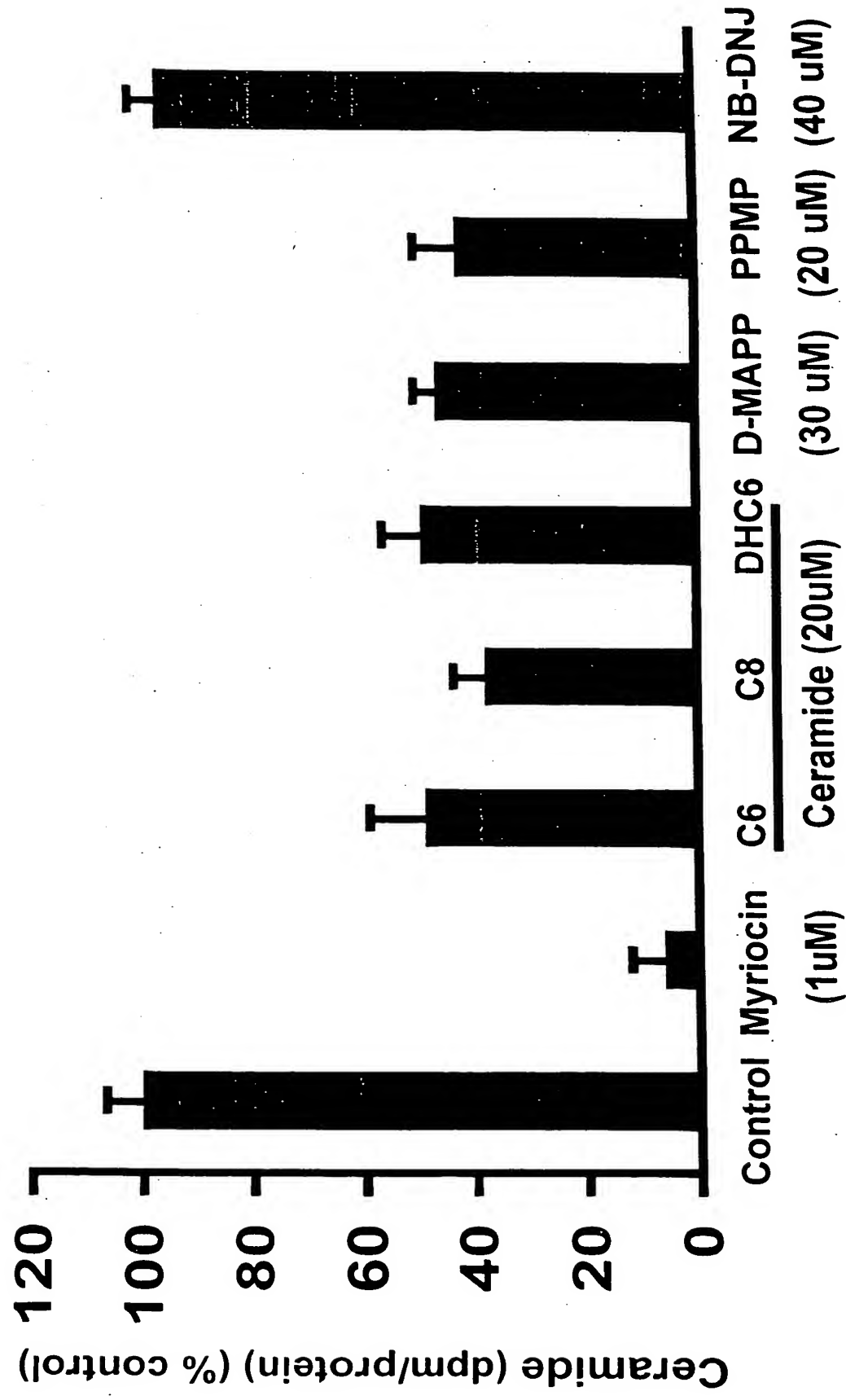


Fig. 2

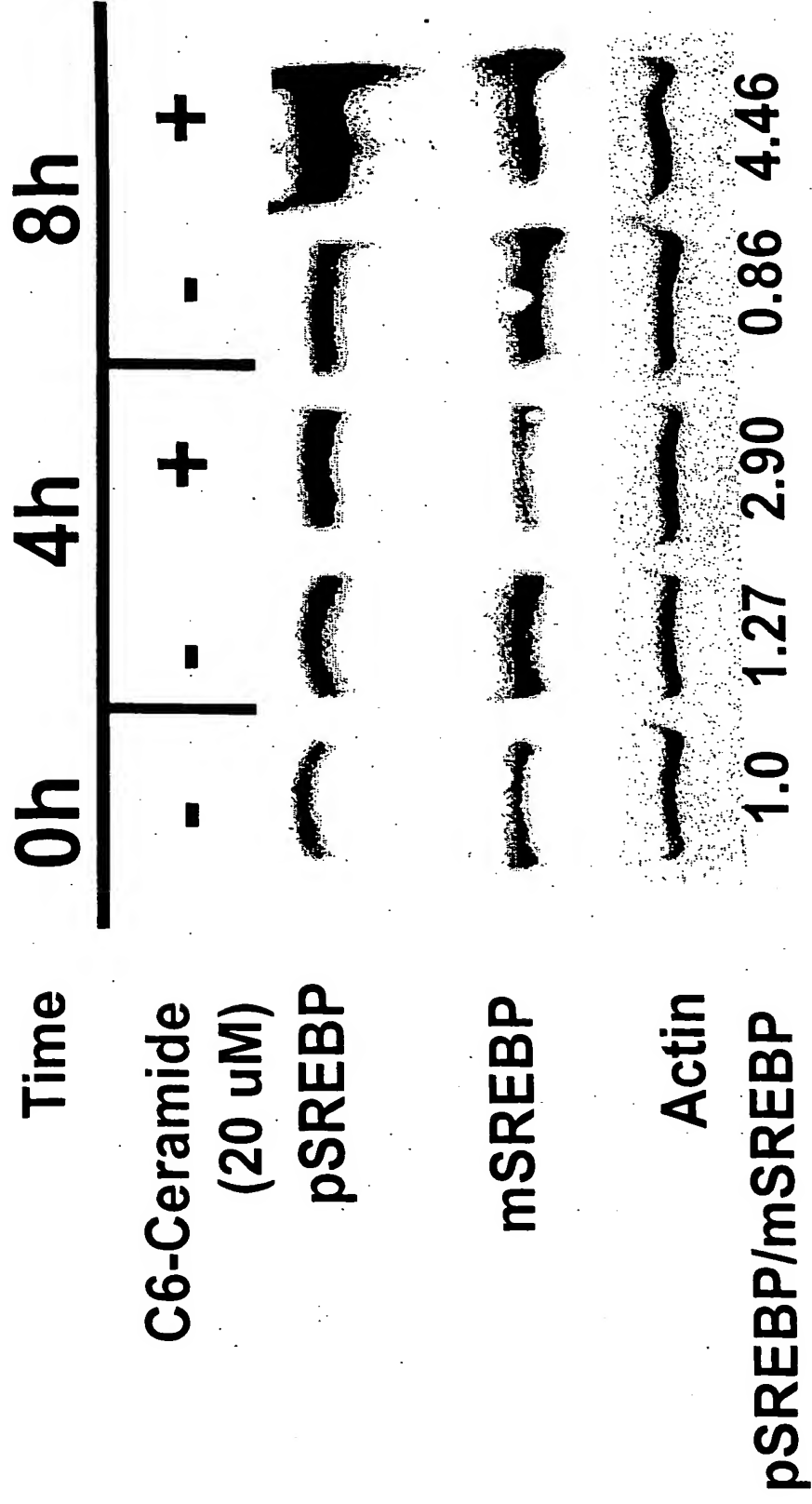


Fig. 3A

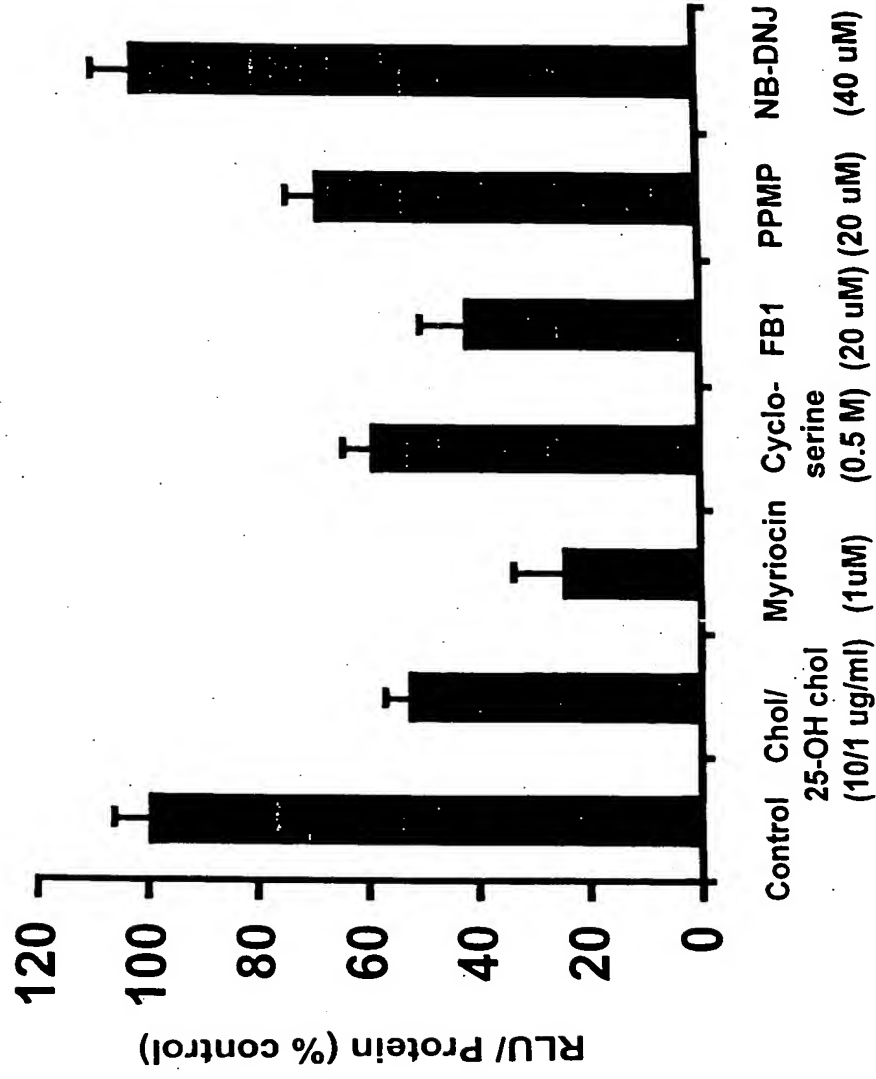
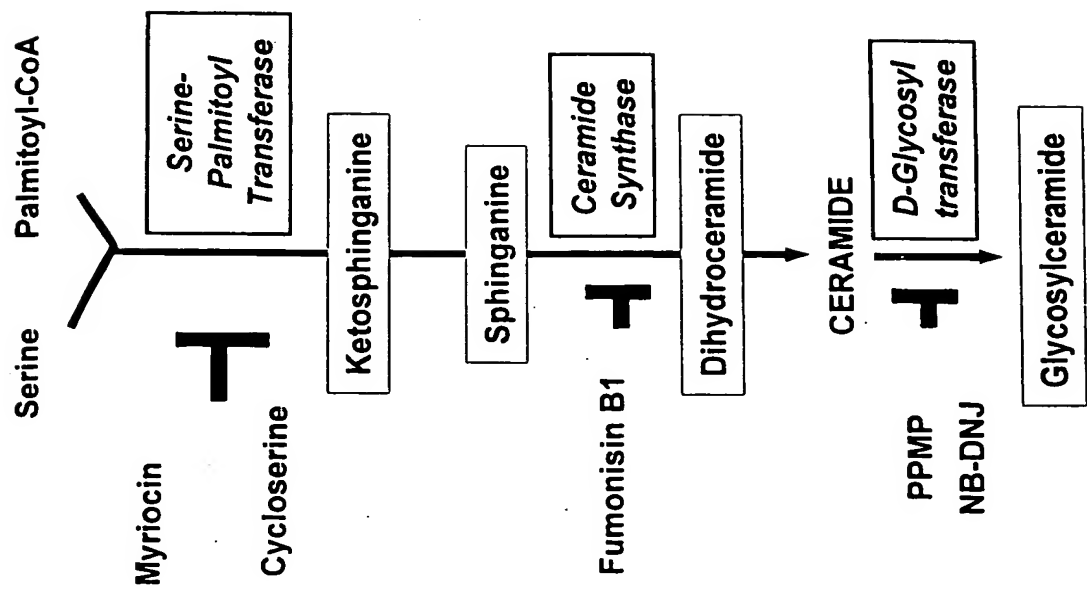


Fig. 3B

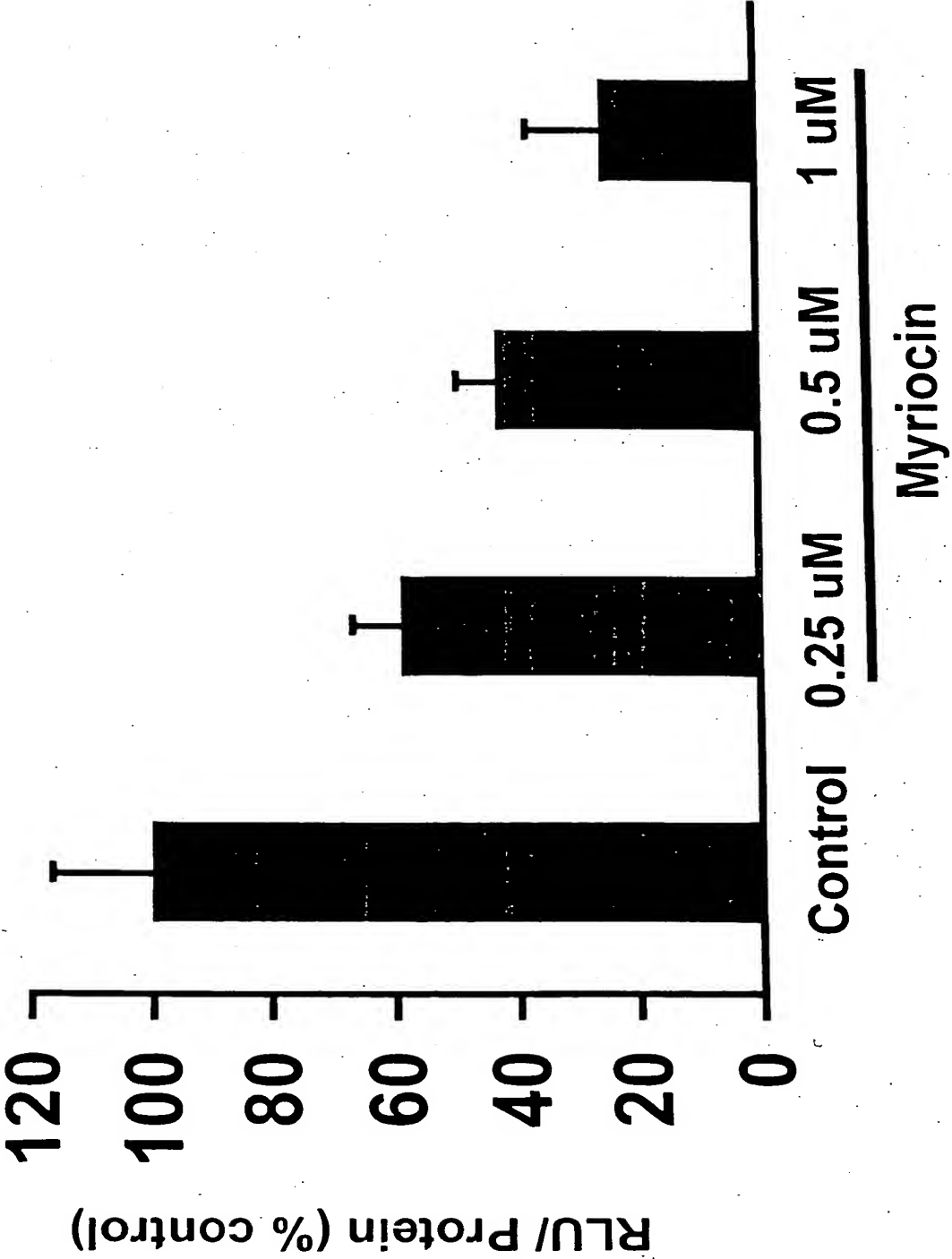


Fig. 4A

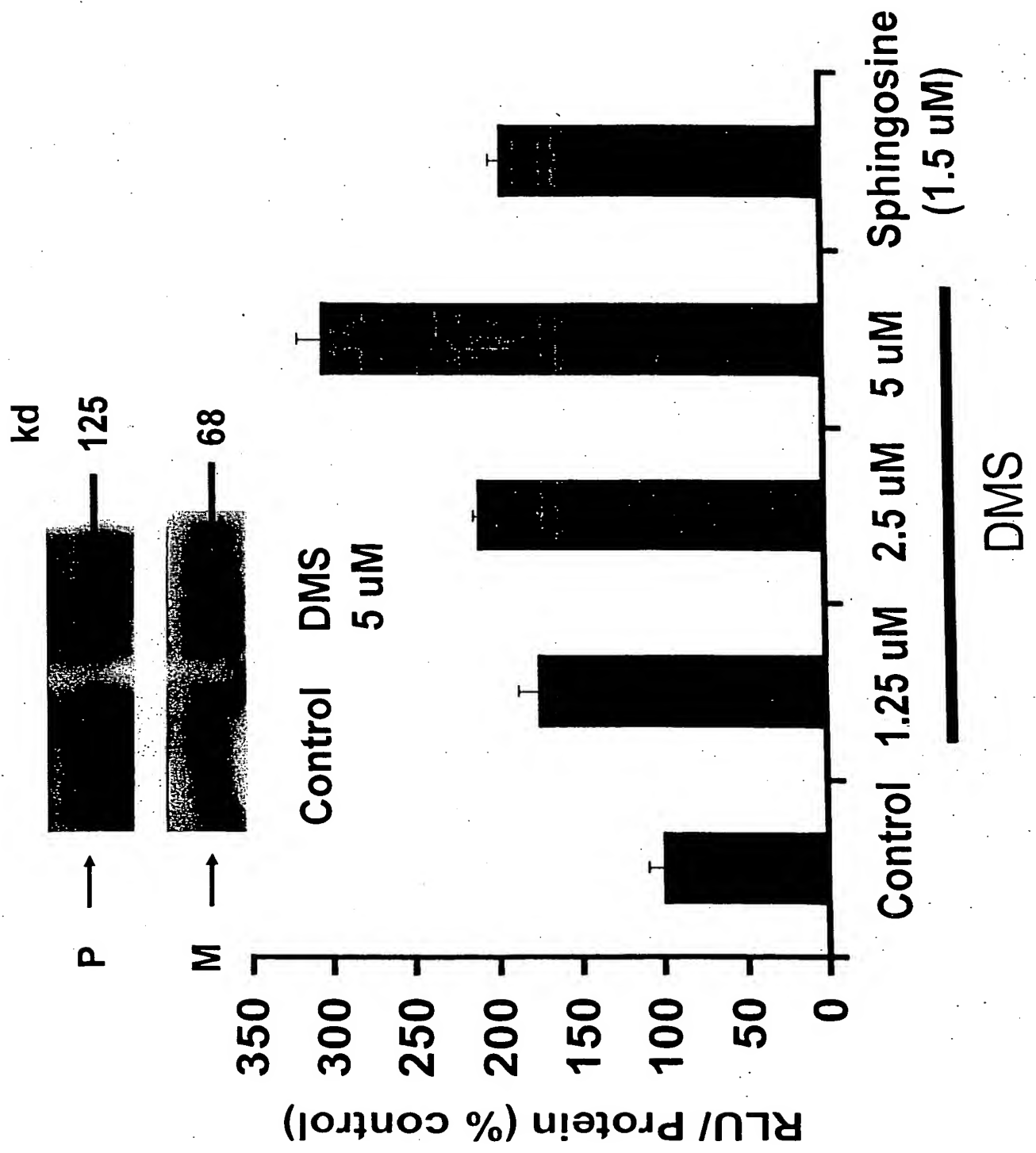


Fig. 4 B

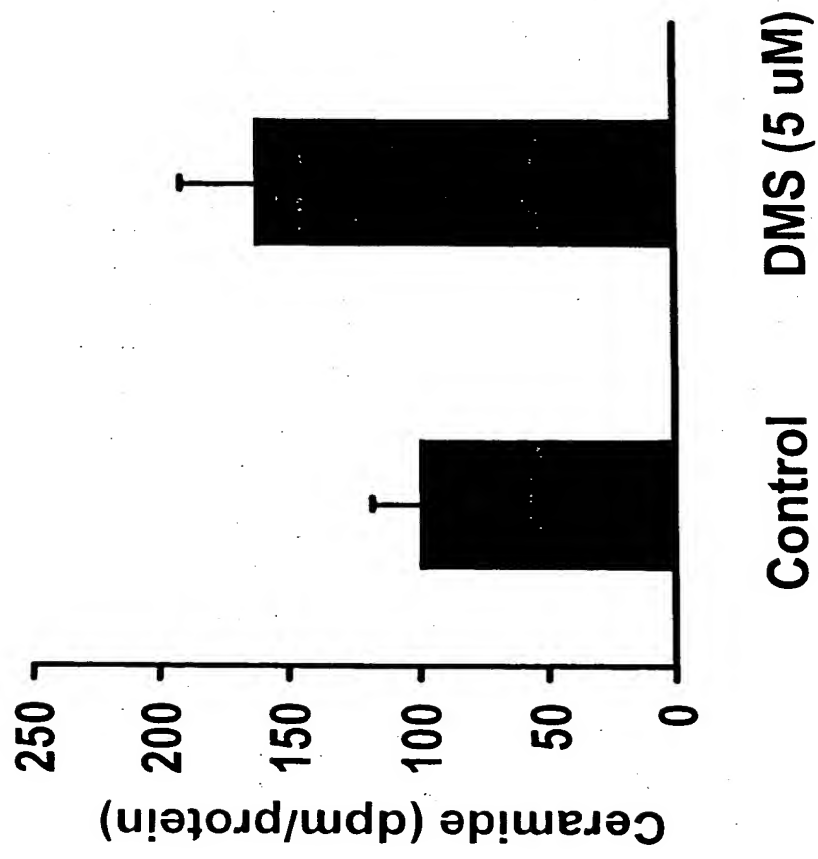


Fig. 5

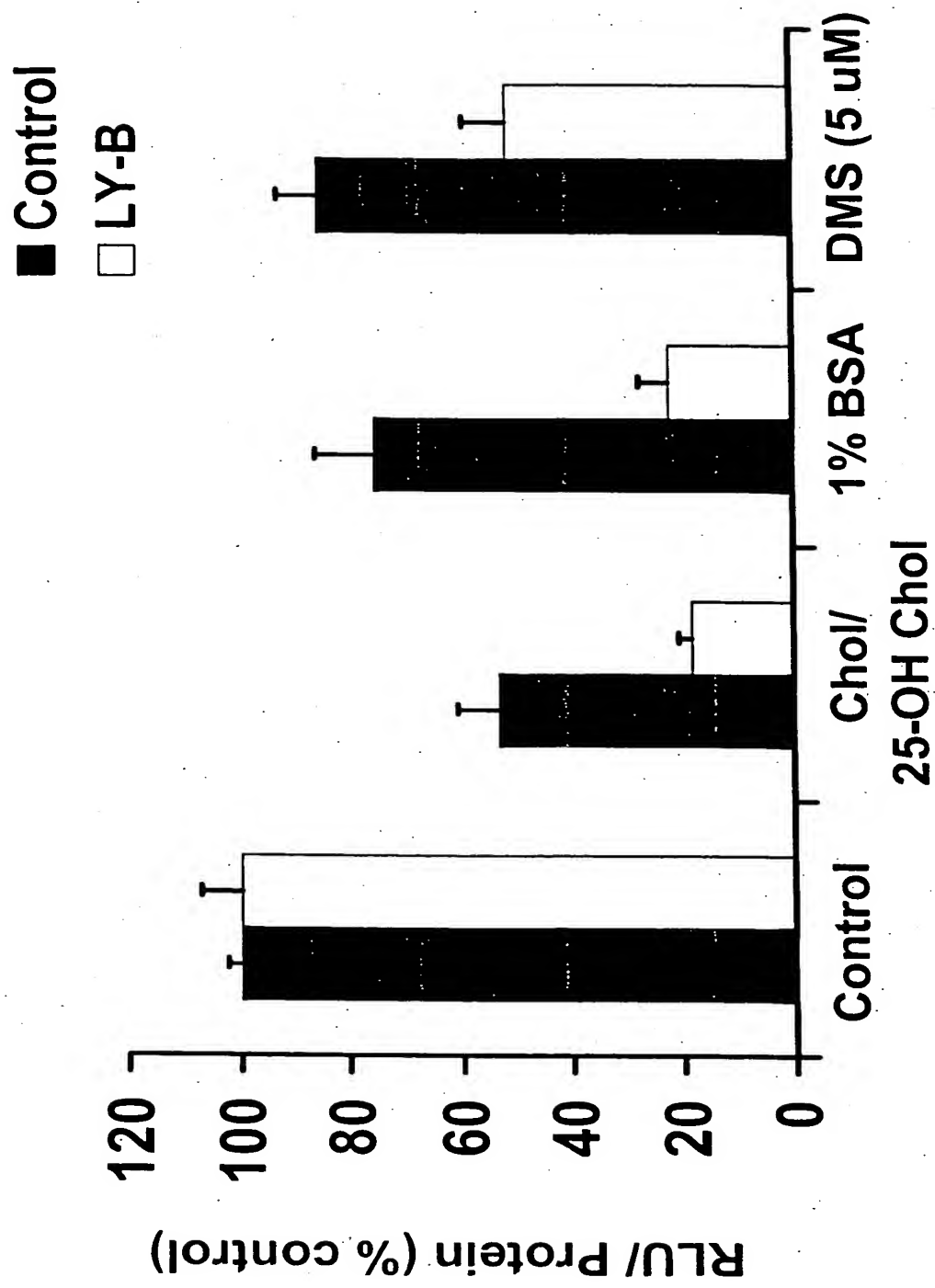
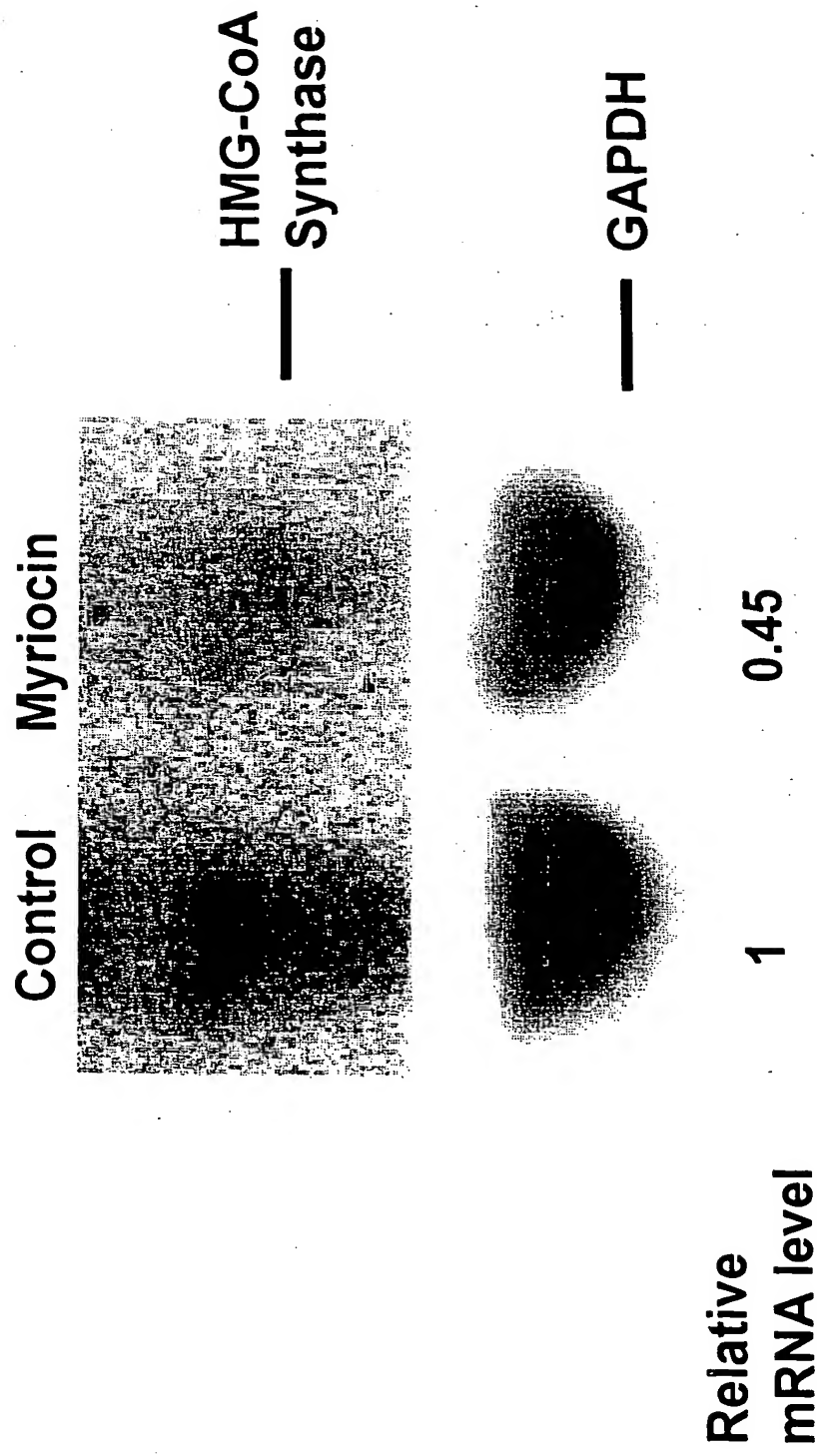


Fig. 6



Overview of compounds used to investigate role of ceramide de-novo pathway in the regulation of SRE-mediated gene transcription.

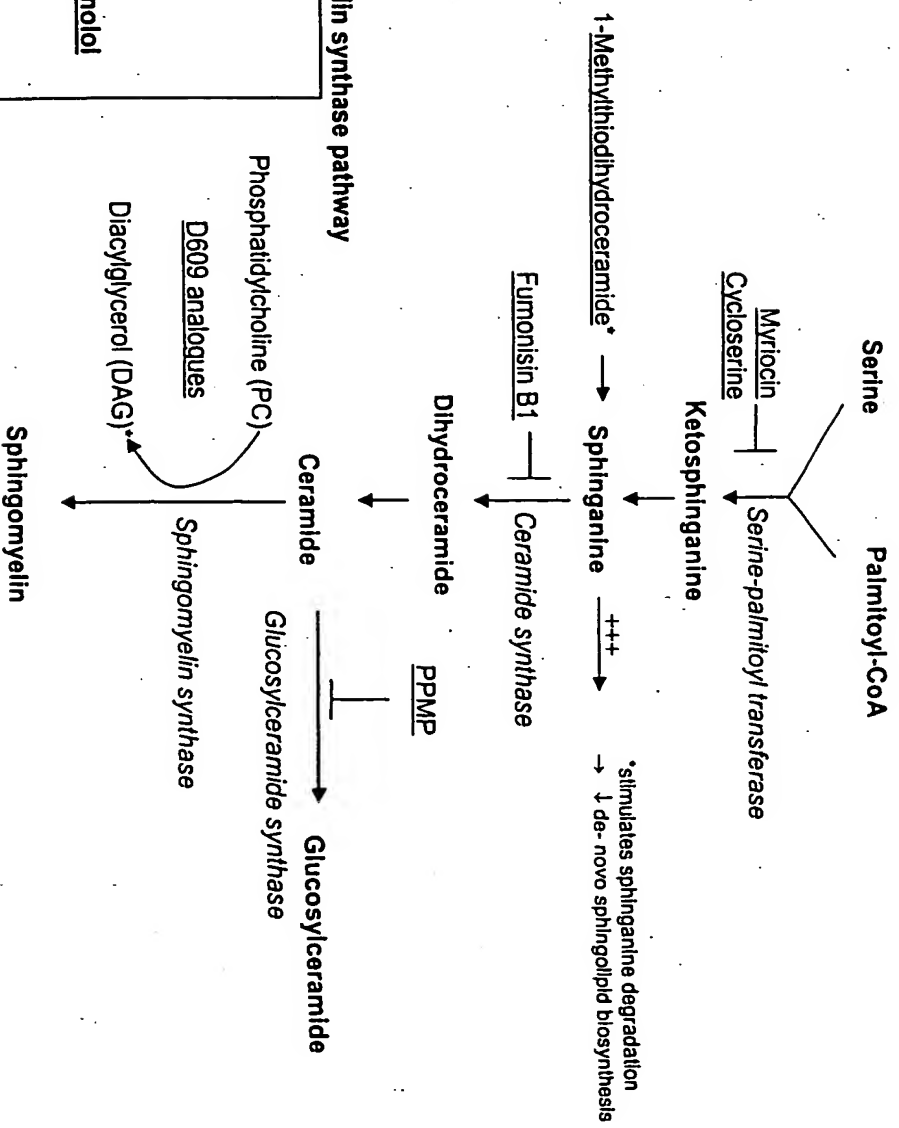
- Inhibitors are underlined

-Enzyme in italics

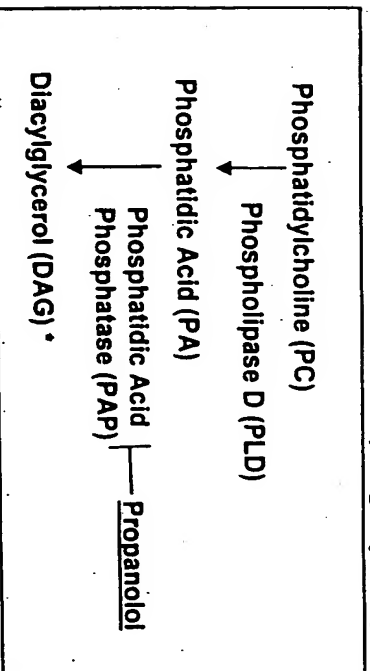
-Alternate pathways that generate DAG and that were investigated are boxed

All inhibitors of ceramide de-novo pathway, c ramide and dihydroceramide decrease ceramide de-novo synthesis and SRE-mediated gene transcription

Ceramide de-novo synthesis pathway



Generation of DAG: Alternative to sphingomyelin synthase pathway



Vesicle budding: Role of PKD and DAG -

Diacylglycerol (DAG) + PKD = vesicle budding from the TGN

Resvaratrol

*DAG: recruits Protein Kinase D to the trans-Golgi network (TGN) by being a target for PKD's C1a domain. PKD is essential for the initiation of vesicle budding (Malhotra, Baron: Science Vol 292, 325 (2002).

FIG 8

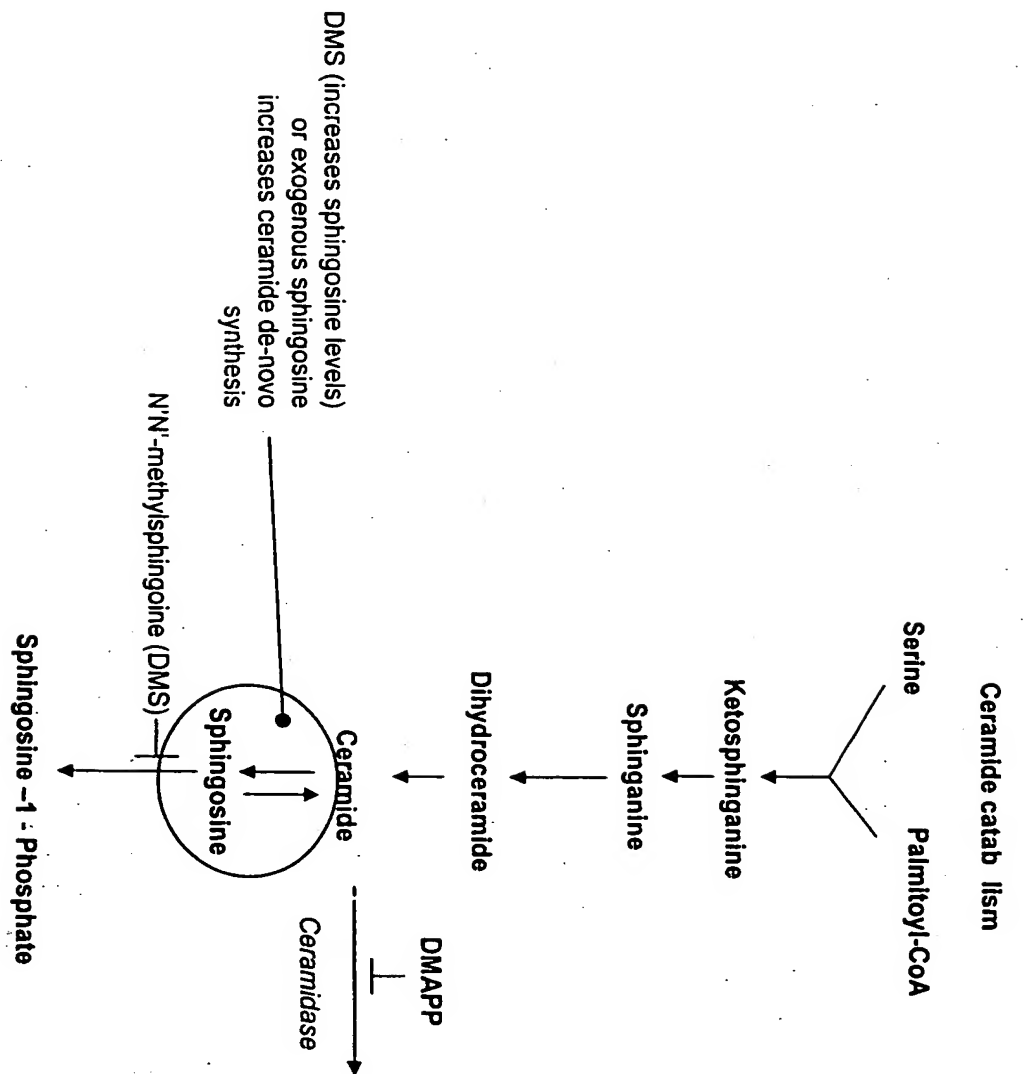


FIGURE 9

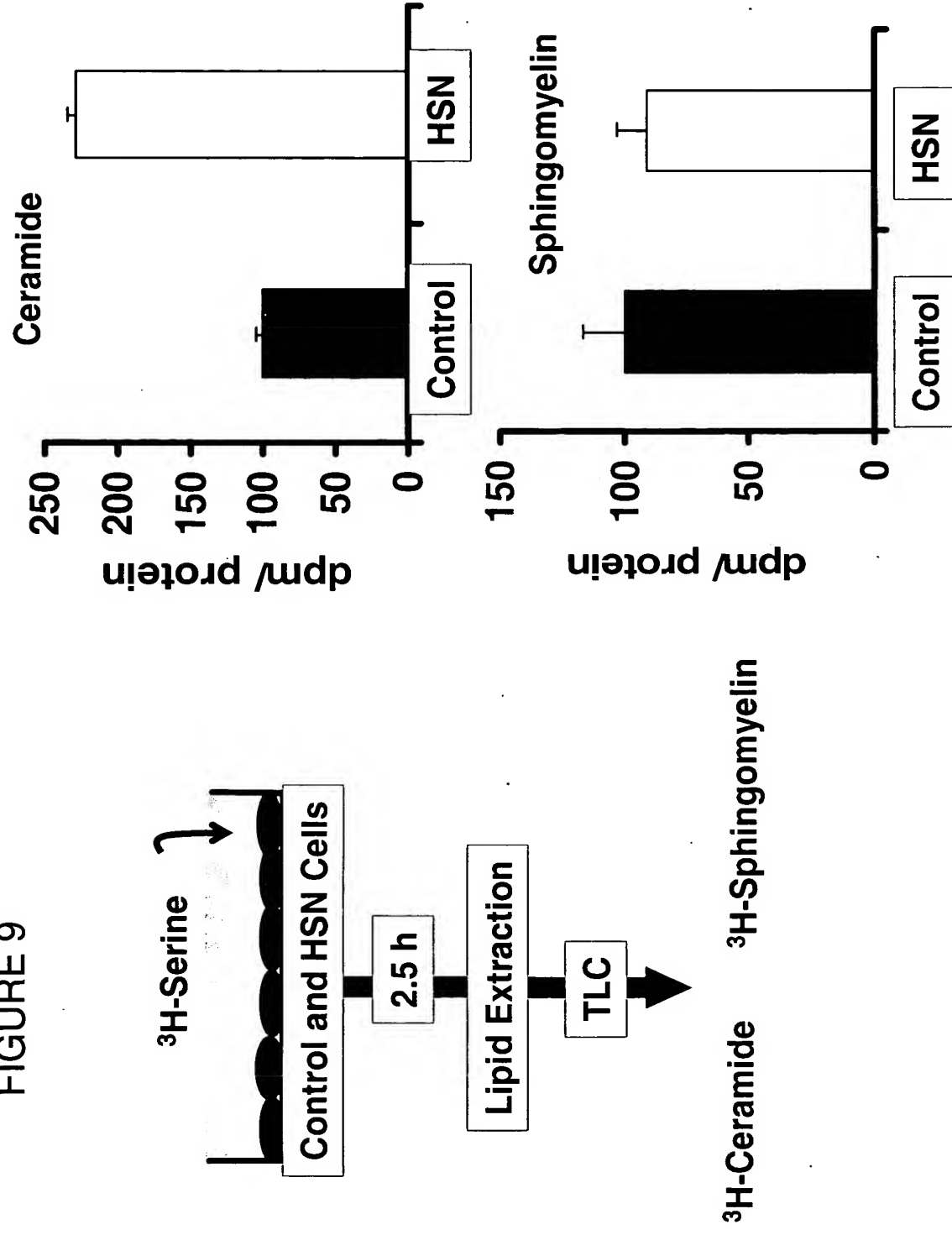
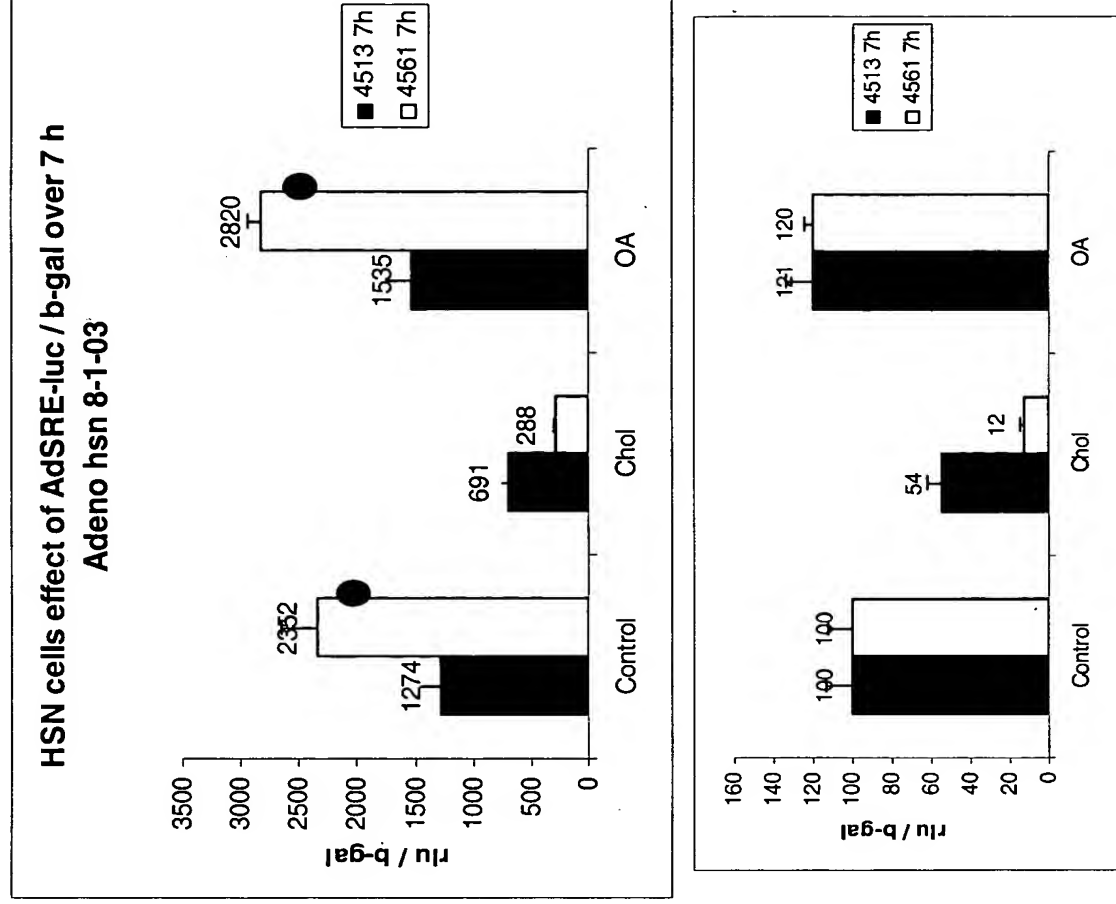
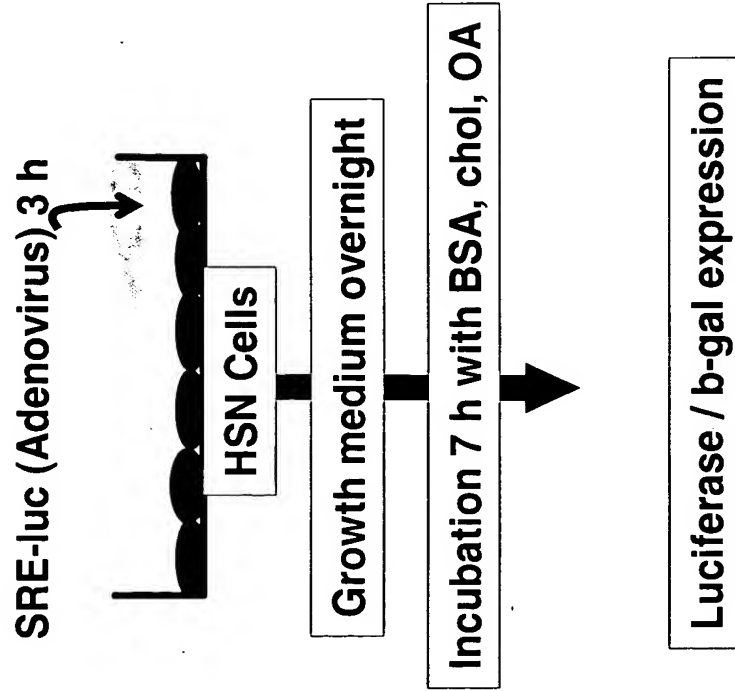


FIGURE 10



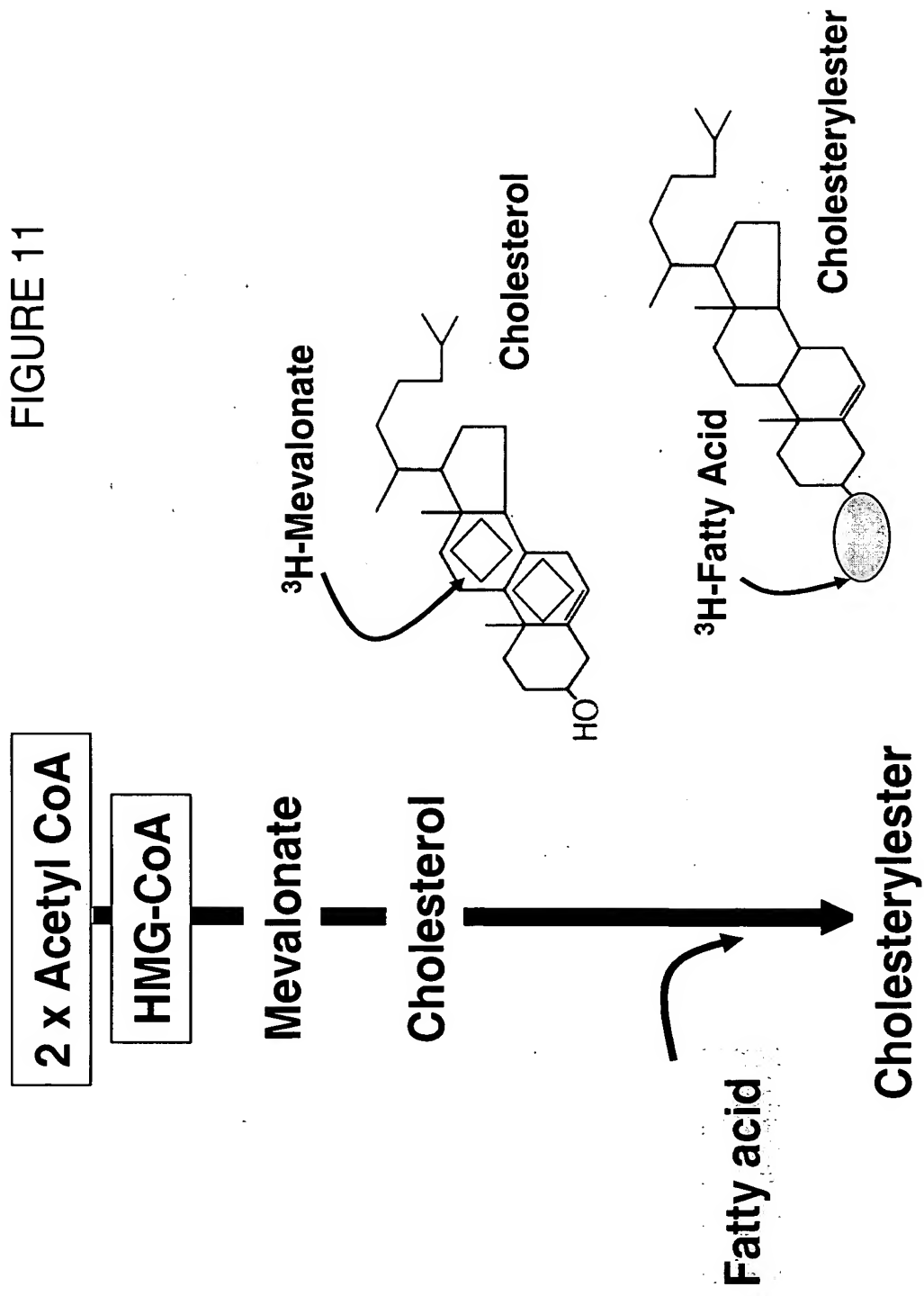


FIGURE 11

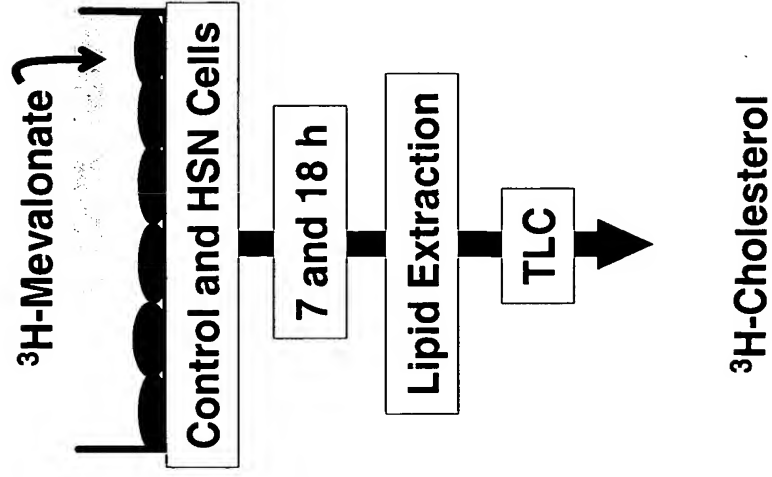
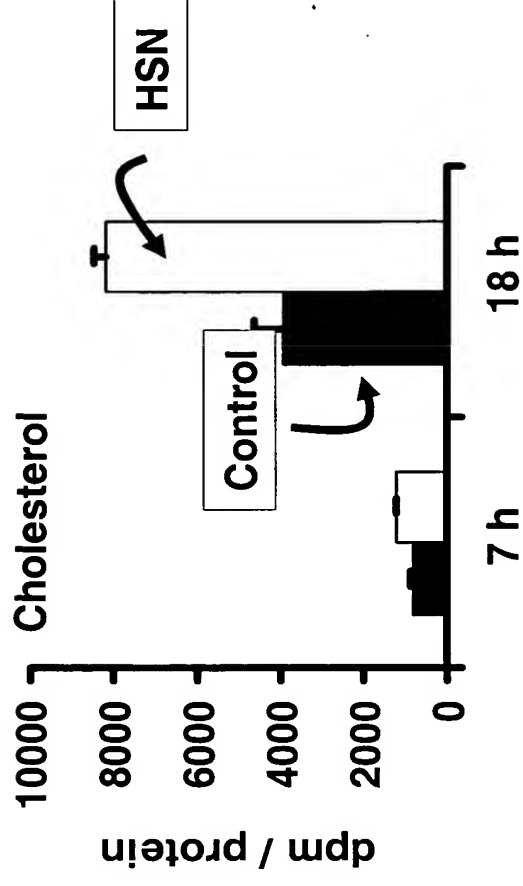


FIGURE 12



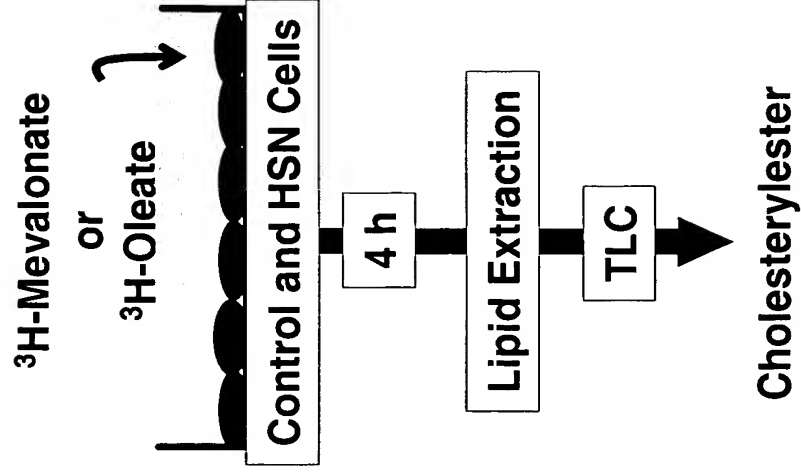
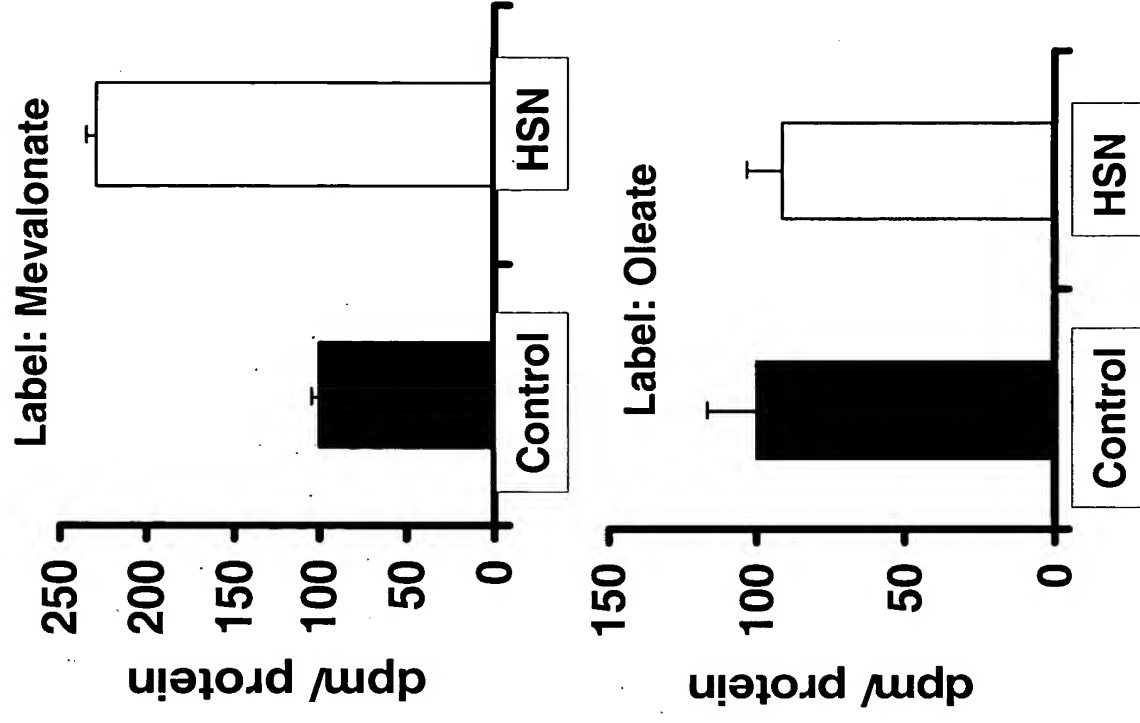


FIGURE 13

FIGURE 14

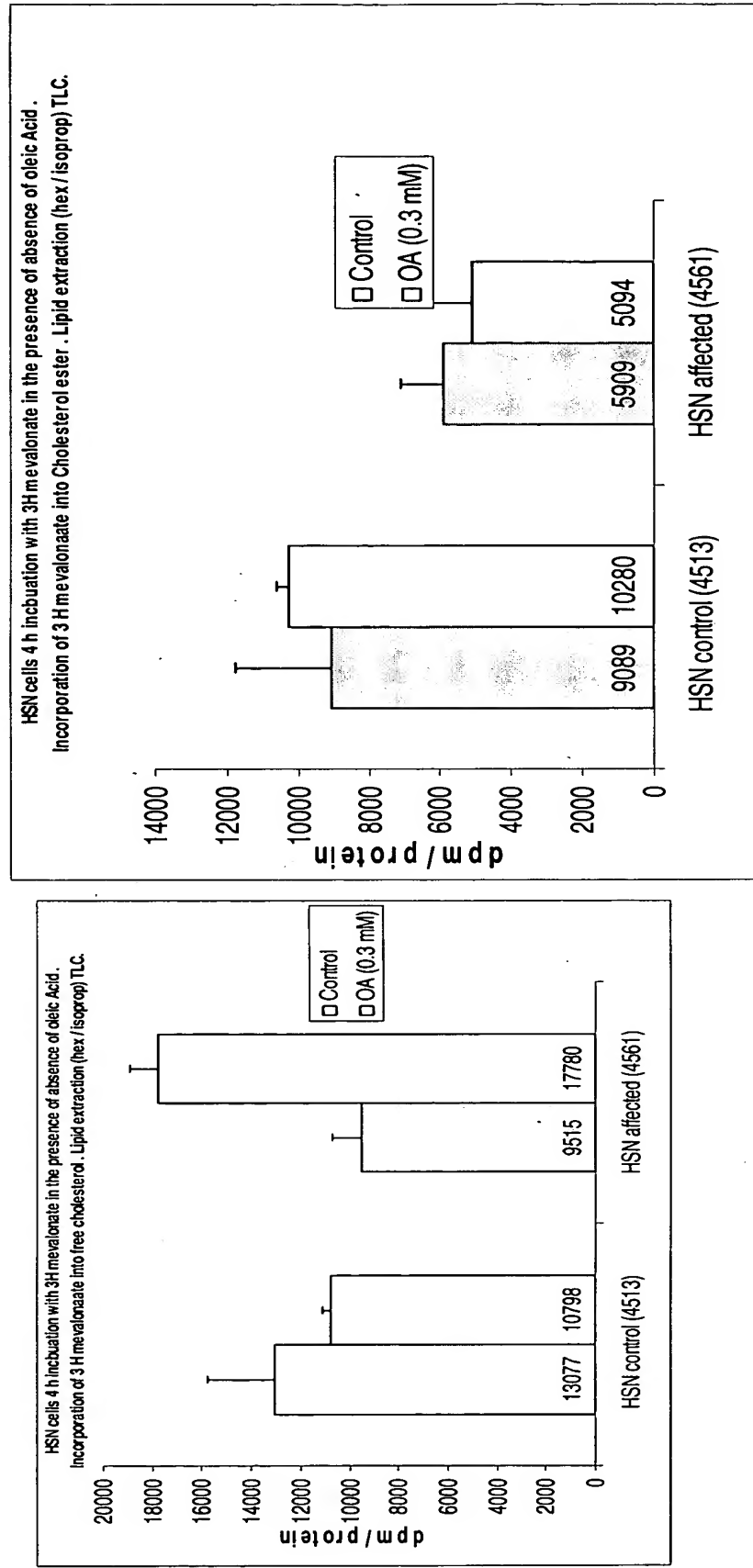


FIGURE 15

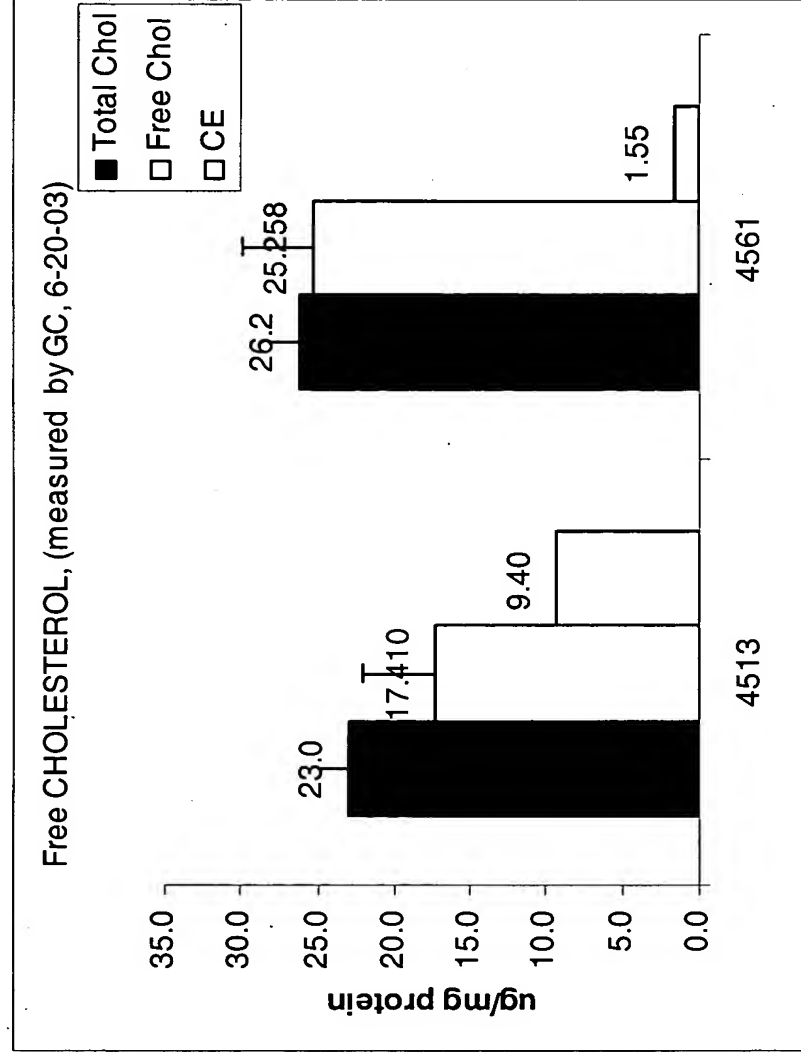


FIGURE 16

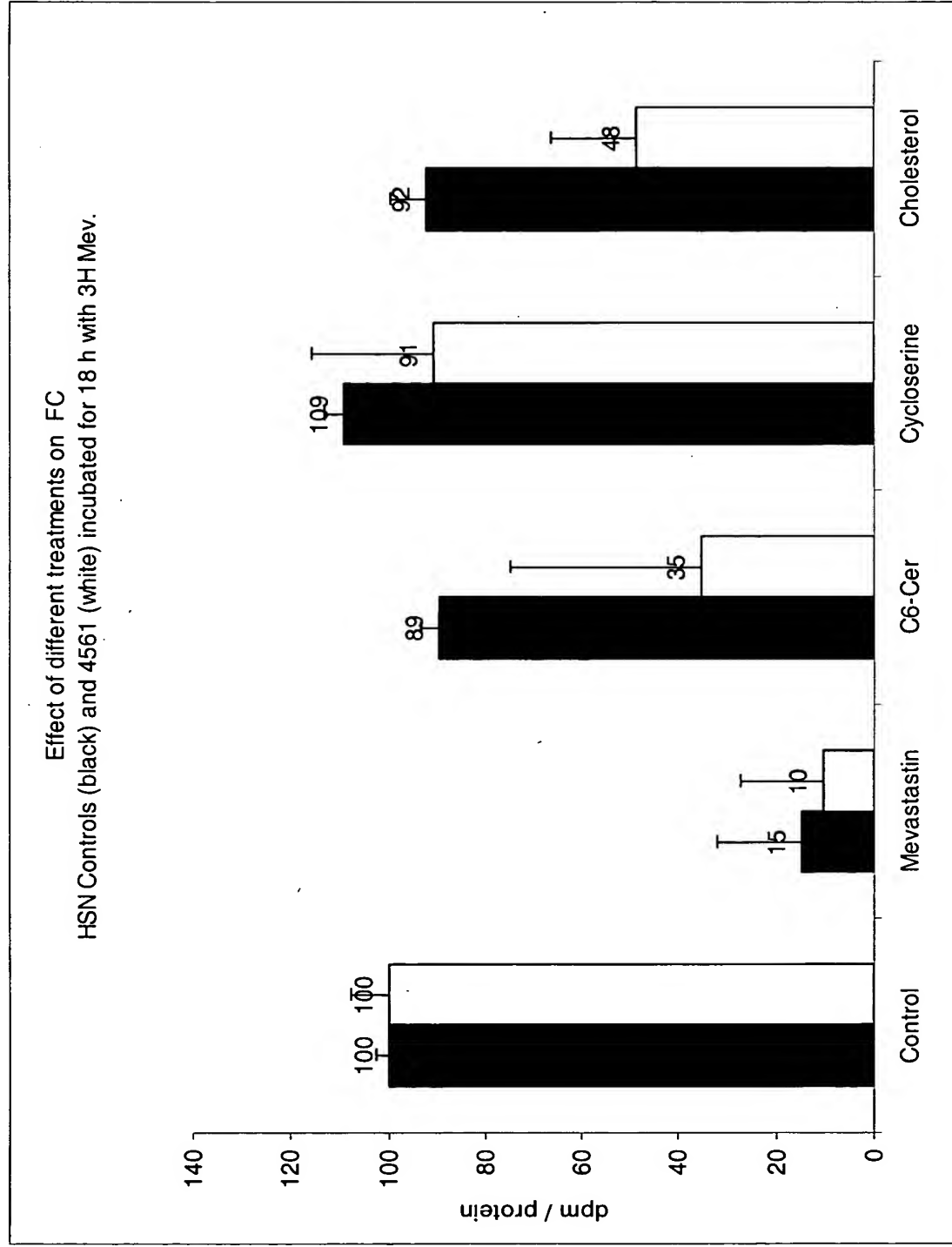


FIGURE 17A

HSN 4513 (control) 4 h with BSA (100 X)



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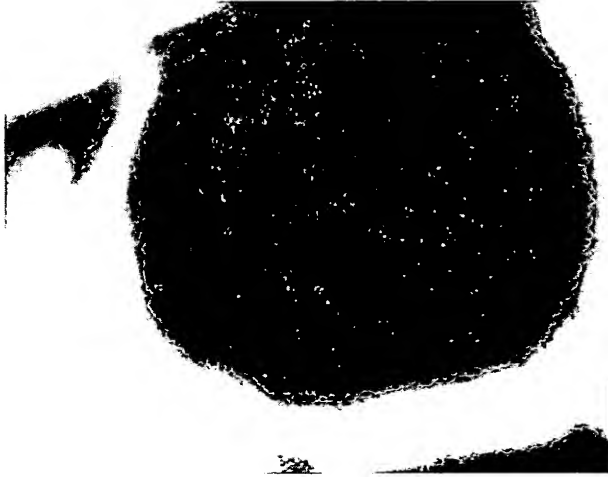
FIGURE 17B

HSN 4513 (control) 4 h with OA (100 X)



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FIGURE 17C



HSN 4561 4 h with BSA (100 X)

FIGURE 17D



HSN 4561, 4 h with 0.3 mM OA (100 X 5-20-03)

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FIGURE 18A

Caspase Assay: Incubation for 16 h. HSN cells in 96 well plate.

■ HSN 4513
□ HSN 4561

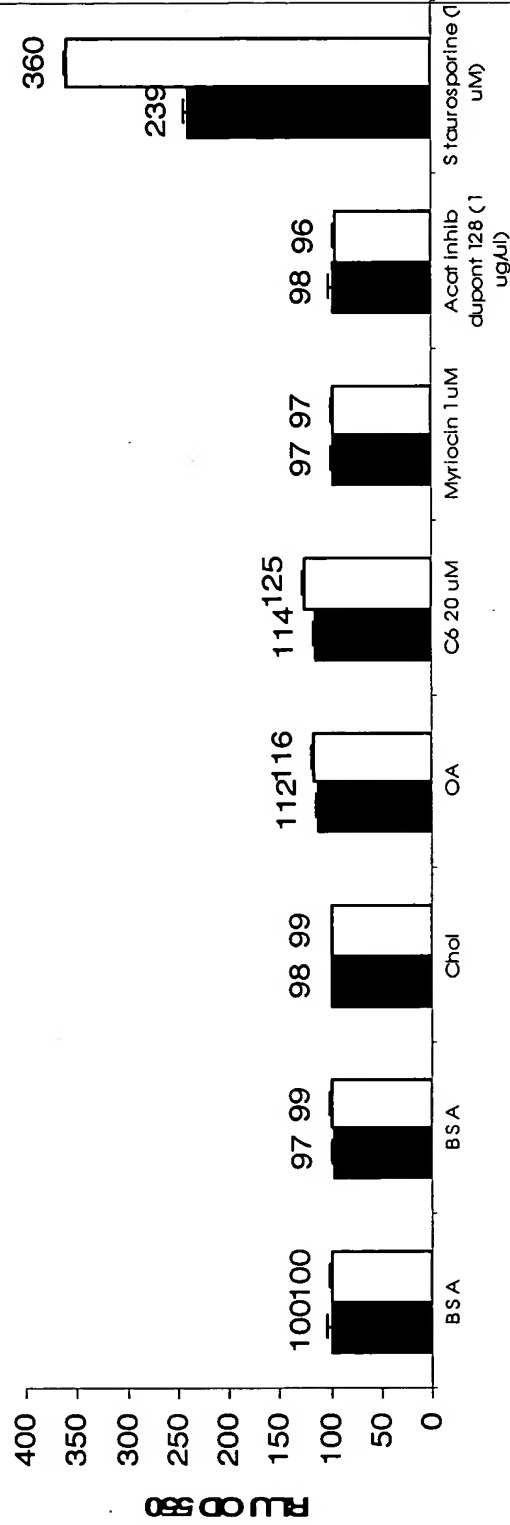


FIGURE 18B

LDH Assay: Incubation for 20 h. HSN cells in 96 well plate.

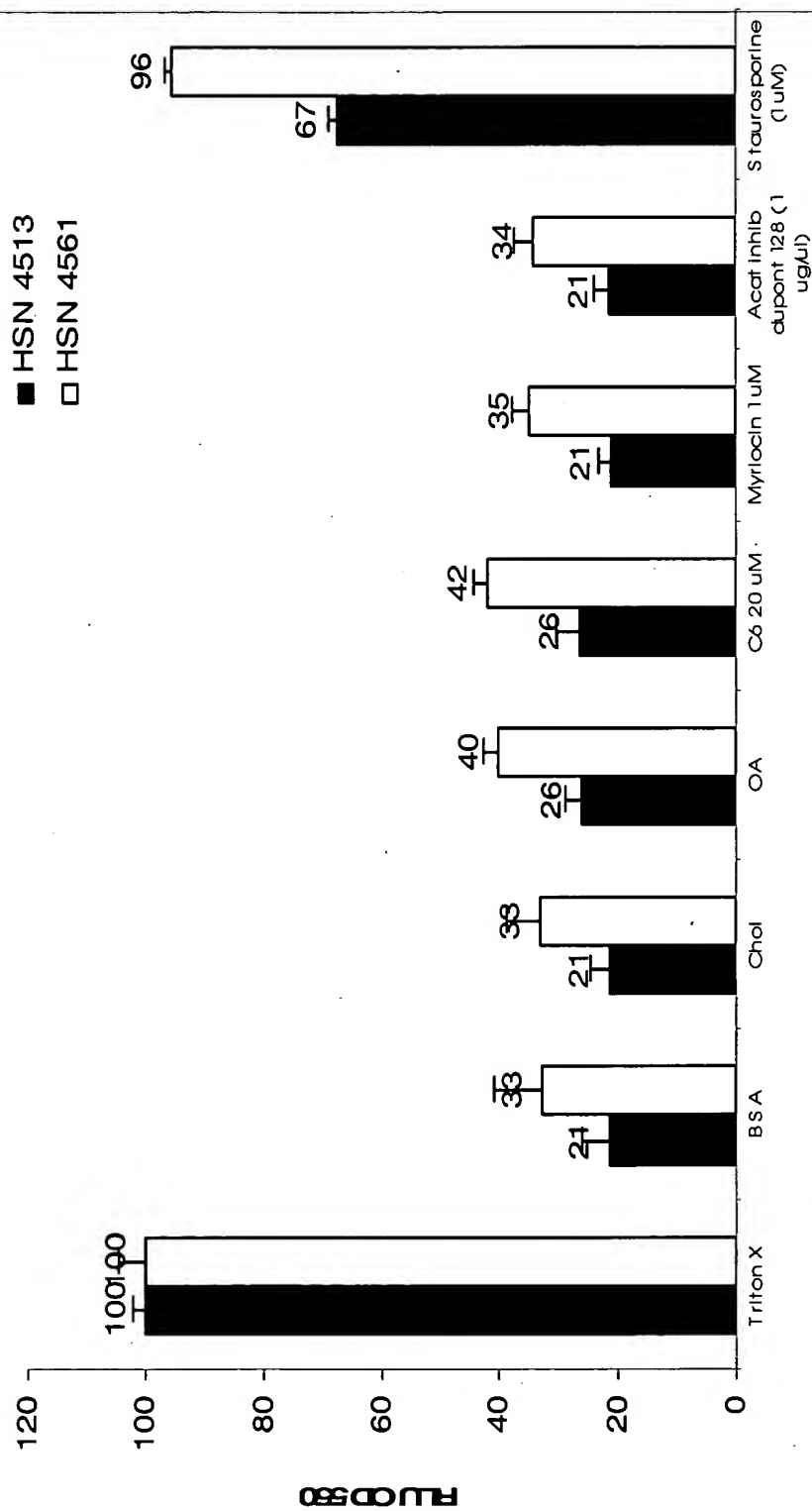


FIGURE 19

Ceramide de novo synthesis (black bars) is increased in NPA cells compared to controls, slightly decreased by cholesterol (grey) and significantly after C8 ceramide (white) for 16 h. Measurement of ^3H serine label over 4 h after o/n treatment

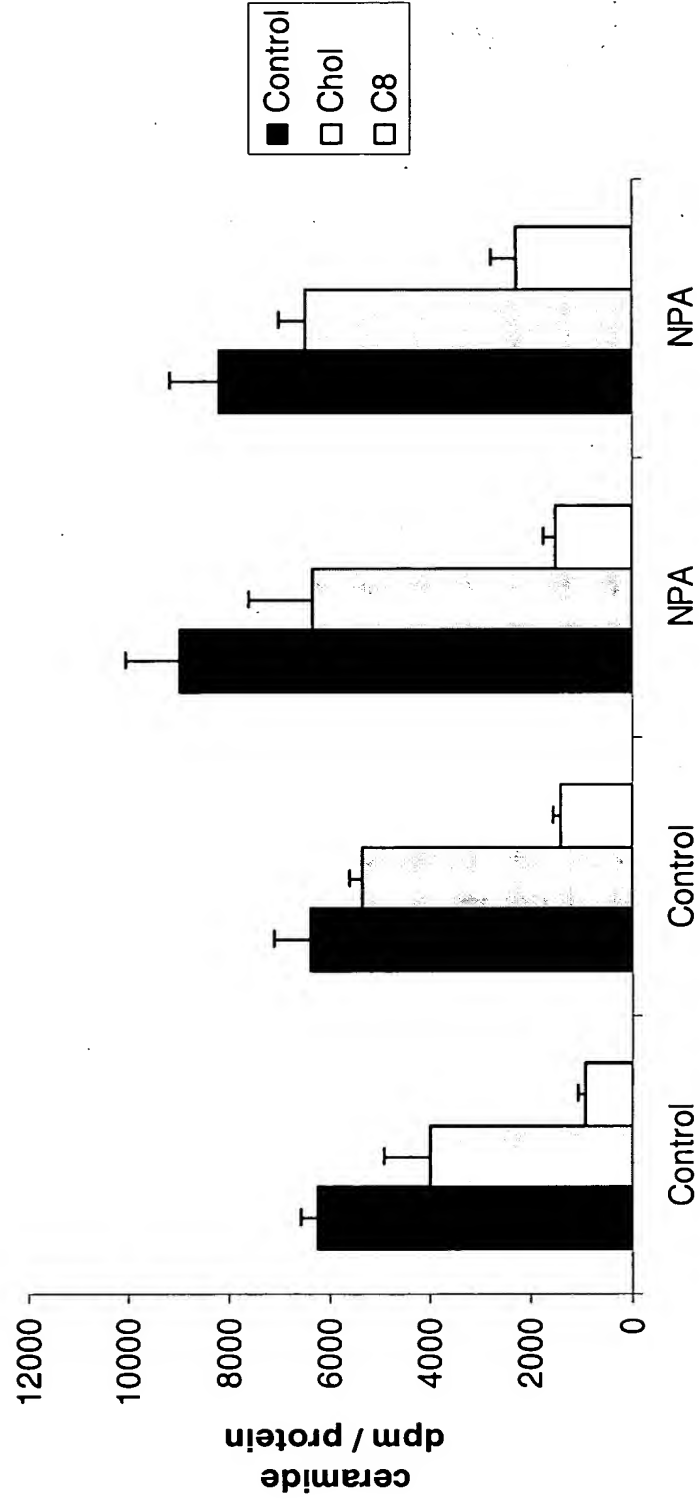


FIGURE 20

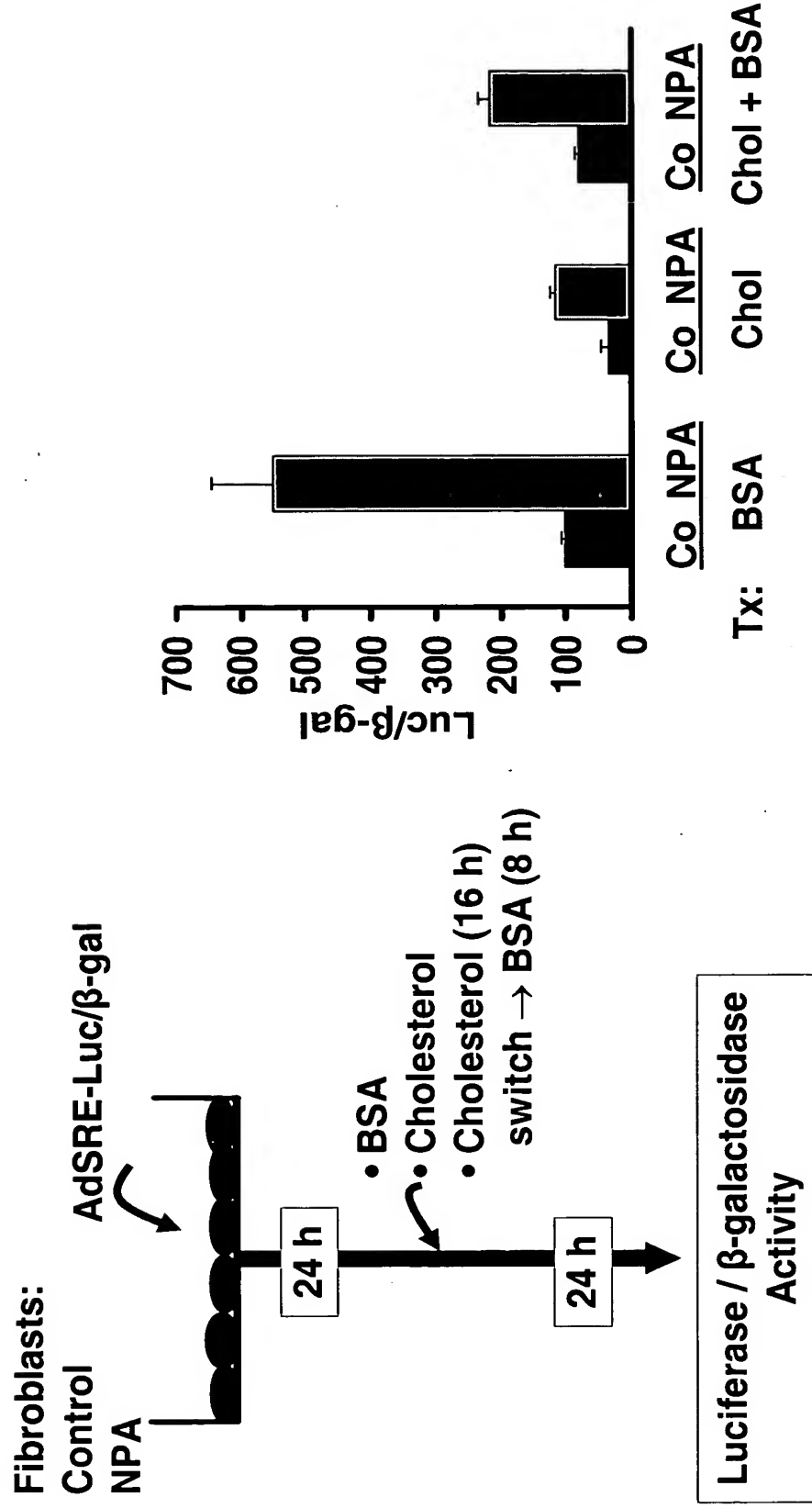


FIGURE 21

Free Cholesterol synthesis (black bars) is increased in NPA cells compared to controls and equally decreased by addition of cholesterol (grey) or C8 ceramide (white) for 16 h. Measurement of ^3H mevalonate label incorporation (lipid extraction, TLC)

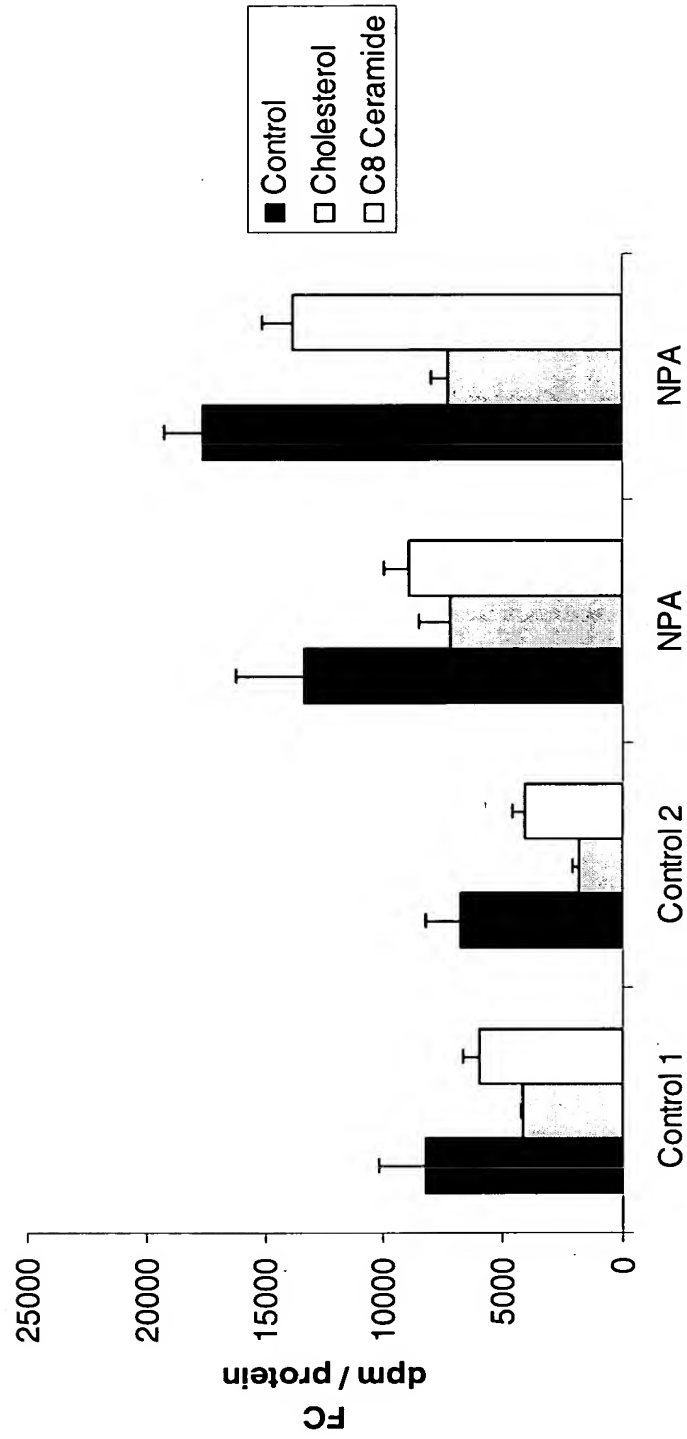


FIGURE 22

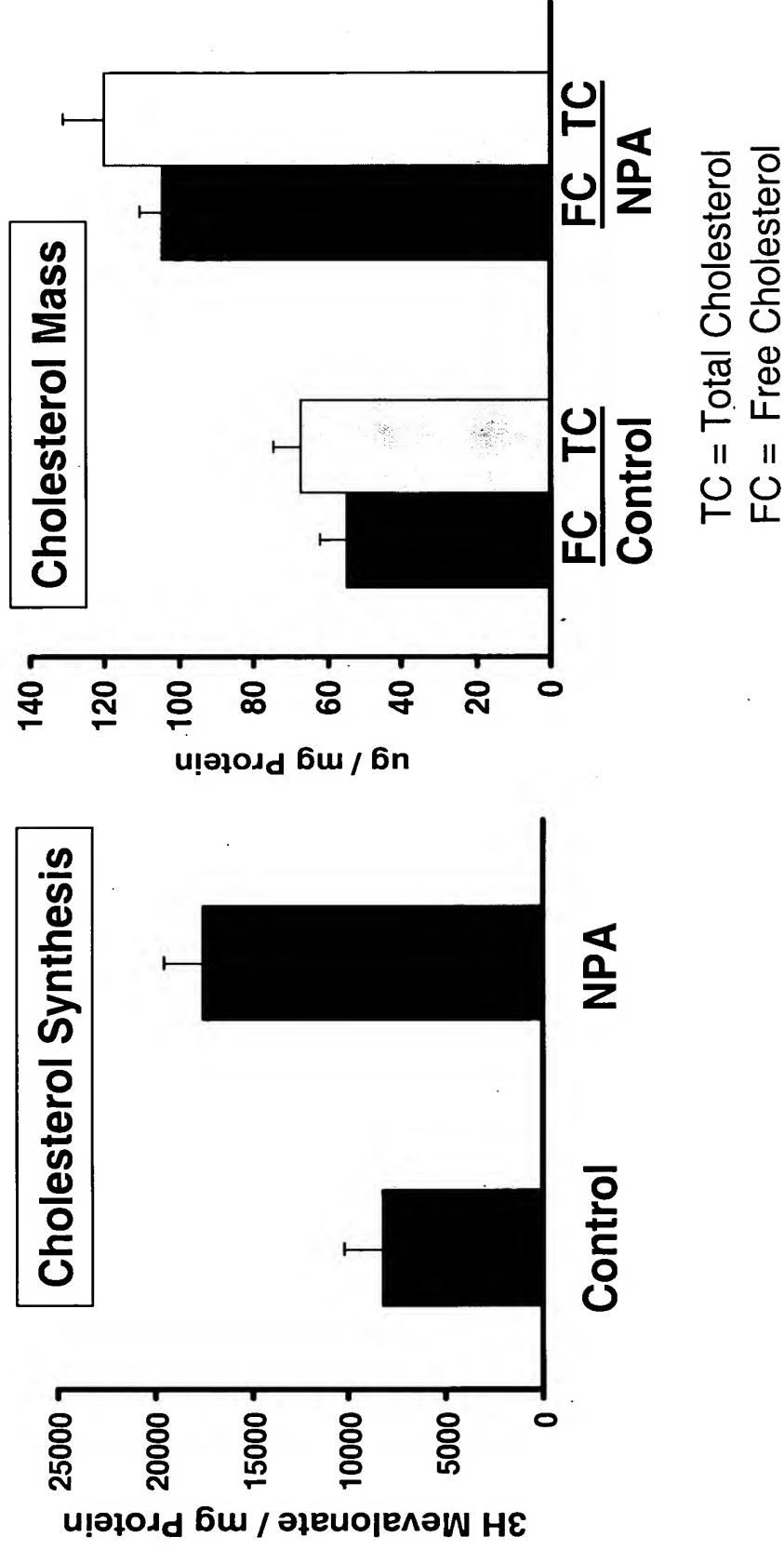


FIGURE 23

